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524 Rec'd PCT/PTO 16 NOV 1999

FORM PTO-1390 (REV 01-98) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		FJN-077
		U.S. APPLICATION NO. (If known) 09/423905
INTERNATIONAL APPLICATION NO. PCT/JP99/01373	INTERNATIONAL FILING DATE 19 March 1999 (19.03.99)	PRIORITY DATE CLAIMED 19 March 1998 (19.03.98)

TITLE OF THE INVENTION

Therapeutic Agent For Preventing and/or Treating Sepsis

APPLICANT(S) FOR DO/EO/US

TANI, Tohru; and KONDO, Hiroyuki

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371 (f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371 (b) and PCT Articles 22 and 39 (1).
4. ☐ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ A translation of the International Application into English (35 U.S.C. 371 (c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3)).
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. ☒ An **unexecuted** oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)) (pages).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☐ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information:

Copy of first page of International Application (1 page);Copy of PCT Request (PCT/RO/101) (4 pages); copy of Notice Informing the Applicant of the Communication of the International Application to the Designated Offices (PCT/IB/308) (1 page); copy of International Search Report (PCT/ISA/210) (2 pages); check in the amount of $840.00; and return postcard.

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17. ☒ The following fees are submitted:	CALCULATIONS	PTO USE ONLY
BASIC NATIONAL FEE (37 CFR 1.492 (a)(1)-(5)		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445 (a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO $970.00		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO. .....$ 840.00		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445 (a)(2)) paid to USPTO. $760.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33 (1)-(4) $670.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33 (1)-(4) $96.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 840.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☒ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$ 0.00	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	1 - 20 =	0	x $ 18.00	$ 0.00	
Independent claims	0 -3 =	0	x $ 78.00	$ 0.00	
MULTIPLE DEPENDENT CLAIM(S)		(if applicable)	+ $ 260.00	$ 0.00	
			TOTAL OF ABOVE CALCULATIONS =	$ 840.00	
Reduction of 1/2 for filing by small entity, if applicable. A Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28).				$ 0.00	
			SUBTOTAL =	$ 840.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +				$ 0.00	
			TOTAL NATIONAL FEE =	$ 840.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property.				$ 0.00	
			TOTAL FEES ENCLOSED -	$ 840.00	
			Amount to be refunded	$	
			charged	$	

a. ☒ A check in the amount of $840.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. in the amount of to cover the above fees.

c. ☒ The Commissioner is hereby authorized to charge any deficiencies required to file the national phase application, not to include surcharges (*e.g.* for an unexecuted declaration), or to credit any overpayment to Deposit Account Number No. 20-0531. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Patent Administrator
TESTA, HURWITZ & THIBEAULT, LLP
125 High Street, High Street Tower
Boston, MA 02110

Signature

Reg. No.: 39,061 Christine C. Vito (NAME) Dated: 16 November 1999

888151_1

Specification

Therapeutic agent for preventing and/or treating sepsis

Technical field

The present invention relates to a therapeutic agent for preventing and/or treating sepsis, comprising Tumor Cytotoxic Factor-II (TCF-II) as an effective ingredient. By the present invention, a therapeutic agent for preventing and/or treating sepsis caused by more than one factor selected from the group consisting of infectious disease, burn, surgery, cancer, acquired immunodeficiency syndrome (AIDS), radiotherapy, chemotherapy, long term total parenteral nutrition (TPN) is provided and useful as a medicine.

Prior art

Sepsis is generally severe systemic infectious disease which developes by continuous or intermittent invasion of bacteria or products secreted by them into blood from bacterial infectious focus present somewhere in tissue or organ of human body. Sepsis is induced by chemotherapy using corticosteroid or antitumor agent, etc., radiotherapy like cobalt radiation, or treatment or operation such as self-retaining catheter, blood dialysis, organ transplantation, heart surgery etc. in a patient with malignant tumor, leukemia, malignant lymphoma, AIDS, collagen disease, renal insufficiency, hepatic disease, cerebrovascular disease or diabetes or in a host with decreased resistance such as humoral immunodeficiency or cellular immunodeficiency of an aged person or an immature infant. Recently, though various kinds of antibiotic have been developed and clinically used for the treatment of sepsis, various kinds of antibiotic-resistant bacterium, such as penicillin- or methicillin-resistant Staphylococcus aureus, emerged, so that mortality rate of patients with sepsis is still about 25 % and many patients die due to sepsis every year.

As bacteria which induce sepsis, in addition to the afore- mentioned antibiotic-resistant bacteria, enterostreptococcus, gram-negative bacillus such as Escherichia coli, Pseudomonas aeruginosa, Klebsiella and Proteus, etc. are exemplified. Among these, a patient with sepsis due to gram-negative bacillus suffers from hyperthermia, chill trepidation, tachycardia, slight depression of blood pressure, depression of peripheral resistance, hyperkinemia, hyperventilation, respiratory alkalosis, hyperlactacidemia and sometimes heart failure at early stage, followed by depression of blood pressure and cardiac output and falling into severe conditions accompanying with metabolic acidosis, consiousness affection, acroagnosis, hypoglycemia and sometimes resulting in death. Therefore, treatment of sepsis is considered to be an important object.

Bacteria are mainly thought to invade into living body by two different kinds of route. One is exogenous case such as intravenous self-retaining catheter or puncture needle used on infusion or supplemental infusion, and the other is endogenous case such as invasion of bacteria widely distributed in human living body such as intestine etc.

Transfer of bacteria or products secreted by them from intestine is called as bacterial translocation or endotoxin translocation and is noticed as a trigger of inducing sepsis. Such a translocation of bacteria and/or products secreted by them from intestine is observed when a patient is severely damaged by burn, major surgery, etc, and when a patient after surgery or a patient with consciousness affection receives long term TPN treatment and becomes serious problems.

For the treatment of sepsis comprising these bacterial translocation, antibiotic treatment is chosen first and recognized to have a certain level of effects. However, antibiotic treatment is thought to have its limit due to its side-effects, appearance of antibiotic-resistant bacteria and its little effects on shock symptom. In addition, supplement of nutrition by infusion or treatment by γ-globulin is carried out but these are aimed for recovery of host immunity and remain as auxiliary treatment for antibiotic treatment. Thus, there is no effective treatment

for sepsis.

Disclosure of the invention

The present inventors have eagerly studied to find out a therapeutic agent for sepsis and found that TCF-II known as tumor cytotoxic factor had an excellent effect for preventing and treating sepsis. Accordingly, an object of the present invention is to provide a therapeutic agent for preventing and/or treating sepsis caused by more than one factor selected from the group consisting of burn, surgery, cancer, AIDS, radiotherapy, chemotherapy and long term TPN, comprising TCF-II as an effective ingredient.

The present invention provides a therapeutic agent for preventing and/or treating sepsis, comprising TCF-II as an effective ingredient. The therapeutic agent of the present invention is useful for preventing and/or treating sepsis caused by more than one factor selected from the group consisting of burn, surgery, cancer, AIDS, radiotherapy, chemotherapy and long term TPN.

TCF-II is an effective ingredient of the present invention, a known protein derived from human fibroblast and has the following properties:

1) Molecular weight (SDS electrophoresis)
under non-reducing conditions; 78,000 ± 2,000 or 74,000 ± 2,000
under reducing conditions; 52,000 ± 2,000 (common band A)
30,000 ± 2,000 (band B)
26,000 ± 2,000 (band C)
2) Isoelectric point; 7.4-8.6

The above TCF-II can be obtained by a method of condensing culture medium of human fibroblast, adsorbing the condensate on ionexchange resin and purifying the eluent by affinity column chromatography (WO90/10651) or by a genetically engineered manipulation (WO92/01053).

TCF-II as an effective ingredient of the present invention can be

TCF-II derived from human fibroblast IMR-90 or TCF-II genetically engineered using microorganism or other cell lines based on the genetic sequence described in patent publication WO90/10651. TCF-II obtained by genetically engineered manipulation described in patent publication WO92/01053 can be also used. In such a case, TCF-II with different polysaccharide chain or without polysaccharide chain due to the difference of host cell or microorganism can be used but TCF-II with polysaccharide chain is preferable. TCF-II obtained by these methods can be condensed and purified by usual isolation and purification method. For example, precipitation using organic solvent, salting-out, gel filtration, affinity chromatography using monoclonal antibody and electrophoresis can be exemplified. Purification by affinity chromatography using monoclonal antibody can use monoclonal antibody described in Japanese Published unexamined patent application No. 97 (1993). Obtained purified TCF-II can be lyophilized or kept freezed. Other substances showing the same activity as TCF-II can be used as the same therapeutic agent. For example, hepatocyte growth factor (HGF; Japanese Published unexamined patent application No. 22526/1988) which is different from TCF-II protein in five amino acids or Purified Scatter Factor (SF; Gherardi and Stocker, Nature, 346, 228 (1990)) can be exemplified.

The therapeutic agent of the present invention for preventing and/or treating sepsis can be administered intravenously, intramuscularly or subcutaneously as injections. These preparations can be produced according to a known pharmaceutical preparation method and pH conditioners, buffers, stabilizers can be added thereto if necessary. Dose of the therapeutic agent of the present invention for a patient depends on degree of symptom, health conditions, age and body weight of a objected patient. Though it is not especially restricted, 0.6-600 mg, preferably 6- 60 mg, of purified TCF-II can be administered once a day for one adult patient.

Brief description of the drawings

Figure 1 shows the effects of TCF-II on model animals of cecum-

punctured sepsis in example 1.

● represents vehicle-administered group and

■ represents TCF-II-administered group

Figure 2 shows the effects of TCF-II on LPS-induced bacterial translocation in example 2.

□ represents vehicle-administered group and

■ represents TCF-II-administered group

Best mode for carrying out the invention

The present invention will be described more specifically by the following examples but these are merely exemplified and the scope of the present invention is not restricted by these examples.

[Preparative example 1]

Purification of TCF-II

According to a method described in WO90/10651 and a method of Higashio et. al. (Higashio, K. et. al., B.B.R.C., vol.170, pp397-404 (1990)), cell was cultured and purified TCF-II was obtained.

That is, 3 x 10^6 human fibroblast IMR-90 (ATCC CCL186) cells were placed in a roller bottle containing 100 ml DMEM medium including 5 % calf fetal serum and cultured by rotating it at the rate of 0.5-2 rpm for 7 days. When the total number of cell reached 1 x 10^7 cells were deprived from the wall by trypsin digestion and collected at the bottom of bottle. And 100g of ceramic with the size of 5 - 9 mesh (Toshiba Ceramic) was sterilized and put therein, which was cultured for 24 hours. After then, 500 ml of the above culture medium was added thereto and the culture was continued. The total volume of culture medium was recovered every 7-10 days and fresh medium was supplemented. Production was kept for 2 months like this and 4 liters of culture medium was recovered per a roller bottle. Specific activity of TCF-II in culture medium obtained as above was 32 μg/ml. Culture medium (750 L) was concentrated by ultrafiltration using membrane filter (MW 6,000 cut; Amicon) and purified by 4-steps chromatography, that

is, CM- Sephadex C-50 (Pharmacia), Con-A Sepharose (Pharmacia), Mono S column (Pharmacia), Heparin-Sepharose (Pharmacia) to yield purified TCF-II.

[Preparative example 2]

Production of recombinant TCF-II

According to a method described in WO92/01053, cell transformed with TCF-II gene was cultured and purified TCF-II was obtained. That is, transformed Namalwa cell was cultured and 20 l of culture medium was obtained. This culture medium was treated by CM-Sephadex C-50 chromatography, Con-A Sepharose CL-6B chromatography and finally HPLC equipped with a Mono S column to yield about 11 mg of recombinant TCF-II.

[Preparative example 3]

Production of pharmaceutical preparation of TCF-II

An example of producing injections of TCF-II obtained preparative examples 1 and 2 was shown below/

(1) TCF-II 20 μg
human serum albumin 100 mg

The above composition was dissolved in citric acid buffer solution with pH 6.03 so that the total volume would be 20 ml.
Then, it was divided into vials containing 2 ml each after sterilization and sealed after lyophilization.

(2) TCF-II 40 μg
Tween 80 1 mg
Human serum albumin 100 mg

The above composition was dissolved in physiological saline solution for injections so that the total volume would be 20 ml.
Then it was divided into vials containing 2 ml each after sterilization and sealed after lyophilization.

(3) TCF-II 20 μg
Tween 80 2 mg

Sorbitol 4 g

The above composition was dissolved in citric acid buffer solution with pH 6.03 so that the total volume would be 20 ml.
Then it was divided into vials containing 2 ml each after sterilization and sealed after lyophilization.

(4) TCF-II 40 μg
Tween 80 1 mg
Glycine 2 g

The above composition was dissolved in physiological saline solution for injections so that the total volume would be 20 ml.
Then it was divided into vials containing 2 ml each after sterilization and sealed after lyophilization.

(5) TCF-II 40 μg
Tween 80 1 mg
Sorbitol 2 g
Glycine 1 g

The above composition was dissolved in physiological saline solution for injections so that the total volume would be 20 ml.
Then it was divided into vials containing 2 ml each after sterilization and sealed after lyophilization.

(6) TCF-II 20 μg
Sorbitol 4 g
Human serum albumin 50 mg

The above composition was dissolved in citric acid buffer solution with pH 6.03 so that the total volume would be 20 ml.
Then it was divided into vials containing 2 ml each after sterilization and sealed after lyophilization.

(7) TCF-II 40 μg
Glycine 2 g
Human serum albumin 50 mg

The above composition was dissolved in physiological saline solution for injections so that the total volume would be 20 ml.

Then it was divided into vials containing 2 ml each after sterilization and sealed after lyophilization.

(8) TCF-II 40 μg

Human serum albumin 50 mg

The above composition was dissolved in citric acid buffer solution with pH 6.03 so that the total volume would be 20 ml.

Then it was divided into vials containing 2 ml each after sterilization and sealed after lyophilization.

[Example 1]

Effects of TCF-II in septic rats made by puncturing cecum

Septic model animals were made by puncturing cecum once with 22G injection needle using 7 week old male SD rats (J. Surgical Research 29, 189-201 (1980)). At 48 hours before making septic model, animals were divided into two groups consisting of a control group which would be administered with vehicle only (vehicle-administered group) (n=15) and a TCF-II-administered group (n=11). They were intravenously administered with vehicle or TCF-II (1000 μg/kg) 5 times every 12 hours. The result of the change of survival rate of animals until 2 days after making septic model was shown in figure 1. As the results, the survial rate on day 2 of TCF-II administered group was significantly higher than that of vehicle administered group, which demonstrated that TCF-II administration significantly increased in the survival rate of septic rats. That is, it was confirmed that TCF-II improved the survival rate of individuals with sepsis.

[Example 2]

Effects of TCF-II administration on LPS-induced bacterial translocation

LPS was intravenously administered in 7 weeks old male ICR mice (5mg/kg). At 30 hours before LPS administration, animals were divided into 2 groups consisting of a control group which would be administered with vehicle only (vehicle-administered group) (n=6) and TCF-II-administered group (n=6). They were intravenously administered with vehicle or TCF-

II (200 μg/kg) 3 times every 12 hours. The result of the number of bacteria detected in mesenteric lymph node at 24 hours after LPS administration was shown in figure 2. The detected number of bacteria in the TCF-II-administered group was significantly lower than that of the control group, which demonstrated that TCF-II administration significantly suppressed LPS-induced translocation of bacteria from intestine.

That is, it was confirmed that TCF-II significantly improved the survival rate against bacterial translocation which can be a trigger of inducing sepsis.

Industrial utility

By the present invention, a therapeutic agent for preventing and/or treating sepsis comprising TCF-II as an effective ingredient is provided. The therapeutic agent of the present invention is useful for preventing and/or treating sepsis caused by more than one factor selected from the group consisting of infectious disease, burn, surgery, cancer, AIDS, radiotherapy, chemotherapy, long term TPN.

What is claimed is:

1. A therapeutic agent for preventing and/or treating sepsis, comprising Tumor Cytotoxic Factor-II (TCF-II) as an effective ingredient.

Abstract

A novel therapeutic agent for preventing and/or treating sepsis is provided. It has an excellent effects on sepsis caused by more than one factor selected from the group consisting of infectious disease, burn, surgery, cancer, AIDS, radiation therapy, chemotherapy and long term TPN.

Figure 1

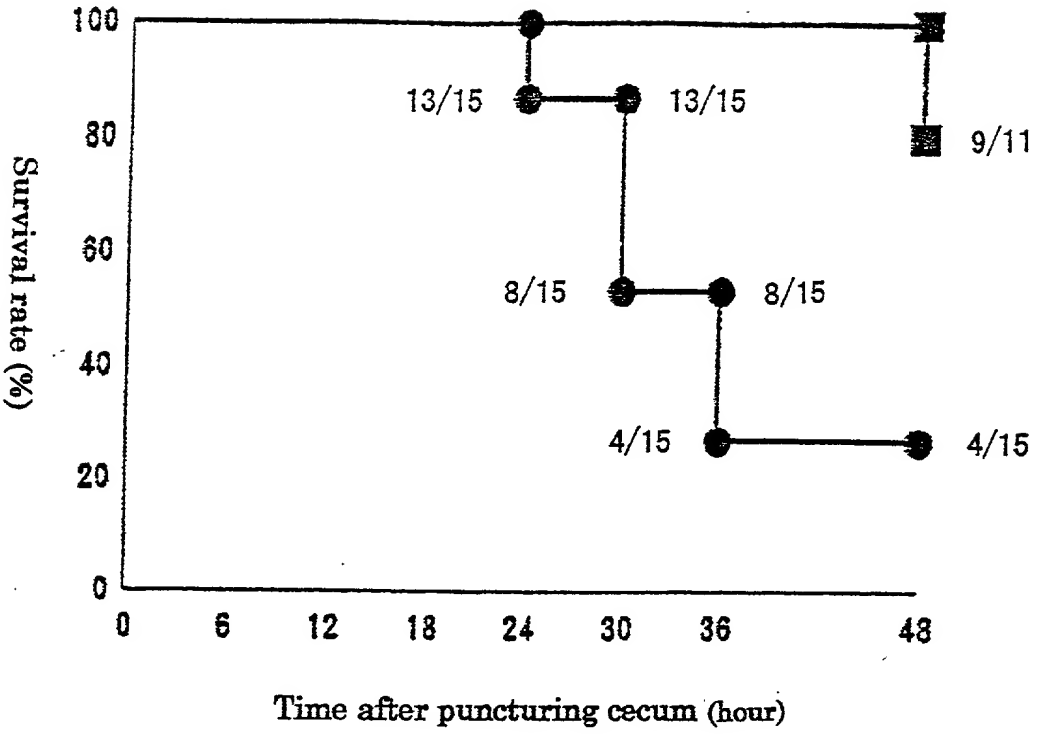
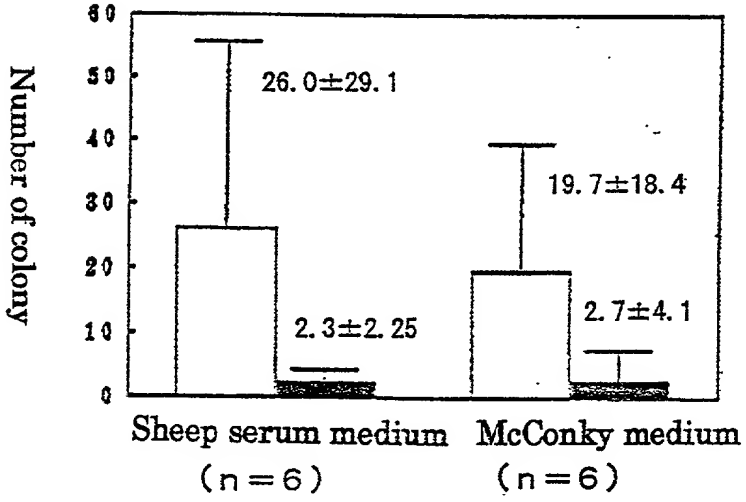


Figure 2



#4

DECLARATION AND POWER OF ATTORNEY FOR UTILITY OR DESIGN PATENT APPLICATION		
	Attorney Docket No.	FJN-077
	First Named Inventor	Tani
	COMPLETE IF KNOWN	
	Application Serial Number	09/423,905
	Filing Date	November 16, 1999
	Group Art Unit	Not yet assigned
	Examiner Name	Not yet assigned

☐ Declaration Submitted with Initial Filing

☒ Declaration Submitted after Initial Filing (surcharge 37 CFR 1.16(e) required)

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Therapeutic Agent for Preventing and/or Treating Sepsis

(Title of the Invention)

the specification of which

☐ is attached hereto

OR

☒ was filed on (MM/DD/YYYY) March 19, 1999 as United States Application Serial Number or PCT International Application Number PCT/JP99/01373 and was amended on (MM/DD/YYYY) _____ *(if applicable).*

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose to the Patent Office all information known by me to be material to patentability as defined in 37 CFR 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	NO
70914/1998	JP	March 19, 1998	☐	☐	☒
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority data sheet attached hereto.

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below.

Application Serial Number(s)	Filing Date (MM/DD/YYYY)	
		☐ Additional provisional application serial numbers are listed on a supplemental priority data sheet attached hereto.

DECLARATION – Utility or Design Patent Application

I hereby claim the benefit under 35 U.S.C. 120 of any United States application(s), or 365(c), of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application or PCT Parent Serial Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number *(if applicable)*
PCT/JP99/01373	March 19, 1999	

☐ Additional U.S. or PCT international application numbers are listed on a supplemental priority data sheet attached hereto.

As a named inventor, I hereby appoint the following registered practitioners to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: ☐ Customer Number

OR

☒ Registered practitioner(s) name/registration number listed below

→ *Place Customer Number Bar Code Label Here*

Name	Registration Number	Name	Registration Number
Steven M. Bauer	31,481	Thomas C. Meyers	36,989
John V. Bianco	36,748	Joseph B. Milstein	42,897
Isabelle A.S. Blundell	43,321	David G. Miranda	42,898
Maureen A. Bresnahan	44,559	Ronda P. Moore	44,244
Michael H. Brodowski	41,640	Edmund R. Pitcher	27,829
Jennifer A. Camacho	43,526	Kurt Rauschenbach	40,137
Joseph A. Capraro, Jr.	36,471	Dianne M. Rees	45,281
John J. Cotter	38,116	Michael A. Rodriguez	41,274
John V. Forcier	42,545	R. Stephen Rosenholm	45,283
Michael J. Giannetta	42,574	J. Scott Southworth	39,382
Duncan A. Greenhalgh	38,678	Christopher W. Stamos	35,370
William G. Guerin	41,047	Joseph P. Sullivan	P-45,349
Ira V. Heffan	41,059	Robert J. Tosti	35,393
Danielle L. Herritt	43,670	Thomas A. Turano	35,722
Mi Kim	44,830	Michael J. Twomey	38,349
Douglas J. Kline	35,574	Christine C. Vito	39,061
John D. Lanza	40,060	Patrick R.H. Waller	41,418
Timothy P. Linkkila	40,702	Daniel A. Wilson	P-45,508
Kurt W. Lockwood	40,704	Yin P. Zhang	44,372

☐ Additional registered practitioners named on supplemental Registered Practitioner Information sheet attached hereto.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor:	☐ A petition has been filed for this unsigned inventor							
Given Name (first and middle [if any])			Family Name or Surname					
Tohru			**TANI**					
Inventor's Signature	Tohru Tani					Date	Feb. 8, 2000	
Residence	City **Kusatsu-shi**	State **Shiga**	Country Japan JPX			Citizenship	**Japanese**	
Post Office Address	**4-3-6, Sakuragaoka, Nojimachi**							
P.O. Address (line 2)	City **Kusatsu-shi**	State **Shiga**	ZIP **525-0055**			Country	**Japan**	
☐ Additional inventors are being named on the _____ supplemental Additional Inventor(s) sheet(s) attached hereto.								

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor							
Given Name (first and middle [if any])			Family Name or Surname					
Hiroyuki			**KONDO**					
Inventor's Signature	Hiroyuki Kondo					Date	Feb. 8, 2000	
Street Address	City **Otsu-shi**	State **Shiga**	Country Japan JPX			Citizenship	**Japanese**	
Post Office Address	**22-46-607, Kayanoura**							
P.O. Address (line 2)	City **Otsu-shi**	State **Shiga**	ZIP **520-2143**			Country	**Japan**	

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor							
Given Name (first and middle [if any])			Family Name or Surname					
Inventor's Signature						Date		
Residence	City	State	Country			Citizenship		
Post Office Address								
P.O. Address (line 2)	City	State	ZIP			Country		